Table I. RX ⟶ RCOOH

RX[a]	Intermediate	Solvent[b]	Cleaving agent	% yield[c,d]
n-$C_5H_{11}Br$	Acyl **3**	THF	O_2	(97)
n-$C_6H_{13}Br$	Acyl **3**	THF	O_2	82
n-$C_{12}H_{25}Br$	Acyl **3**	THF	NaClO	65
n-$C_{12}H_{25}Br$	Alkyl **2**	THF	O_2	84
n-$C_{12}H_{25}Cl$	Alkyl **2**	MP	O_2	84
n-$C_{12}H_{25}Br$	Alkyl **2**	MP	I_2–H_2O	78
$ClCH_2(CH_2)_4CH_2Br$	Acyl **3**	THF	O_2	84[e]
$C_6H_{13}CHBrCH_3$	Acyl **3**	MP–THF	O_2	44 (68)[f]

[a] Used 1–10 mmol of RX, slight excess of $Na_2Fe(CO)_4$, 10 psi of CO for acyl. [b] MP, *N*-methyl-2-pyrrolidone. [c] Products characterized by ir, pmr, melting points, and for new compounds by elemental analysis. [d] Yields in parentheses by glpc using a calibrated internal standard. Other yields for isolated products after recrystallization or distillation. [e] Product 7-chloroheptanoic acid. [f] Yield of the acyl as determined by glpc by quenching with acetic acid to form the aldehyde.

routes.[10] Secondary tosylates give yields comparable to those obtained with primary substrates *via* the acyl routes in THF. With secondary bromides gc yields drop to around 50%; secondary iodides and cyclohexyl or cyclopentyl halides and tosylates give even lower yields.

Table II. RX ⟶ ester or amide

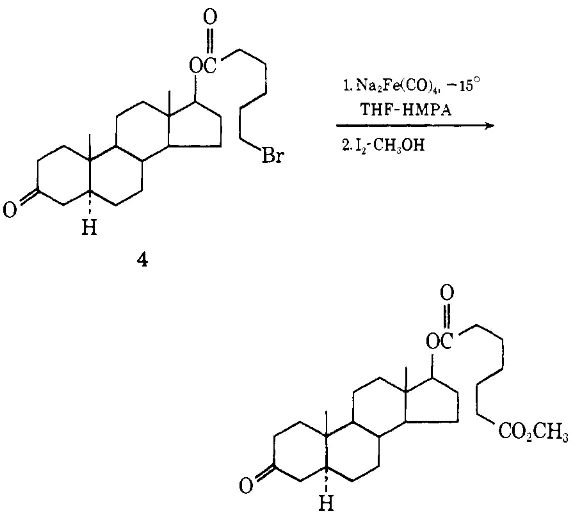
RX[a]	Intermediate	Solvent[b]	Product[c]	% yield[d]
n-$C_8H_{17}Cl$	Alkyl **2**	MP	n-$C_8H_{17}CO_2C_2H_5$	89 (96)
n-$C_8H_{17}Br$	Alkyl **2**	THF–HMPA	n-$C_8H_{17}CO_2C_2H_5$	88 (99)
n-$C_8H_{17}Br$	Acyl **3**	THF	n-$C_8H_{17}CO_2C_2H_5$	84 (99)
$CH_3(CH_2)_5CH(CH_3)OTs$	Acyl **3**	THF	$CH_3(CH_2)_5CH(CH_3)CO_2C_2H_5$	(85)
$BrCH_2(CH_2)_2CH_2CO_2C_2H_5$	Alkyl **2**	THF–HMPA	$H_3CO_2CCH_2(CH_2)_2CH_2CO_2C_2H_5$	(95)
n-$C_5H_{11}Br$	Acyl **3**	THF	n-$C_5H_{11}CON(C_2H_5)_2$	(80)

[a–d] Same as Table I; 15% HMPA.

Polar solvents such as HMPA and *N*-methyl-2-pyrrolidone (MP) allow less reactive substrates such as alkyl chlorides to be used, but in these solvents alkyl migration is inhibited. Hence alkyl routes are preferred in such cases. Benzylic halides alkylate readily, but migration to form the acyl is slow even in THF; nevertheless high yields may be obtained using the alkyl routes in THF.

These reactions exhibit remarkable selectivity. In THF primary bromides react with **1** at a rate $>10^4$ faster than the corresponding chlorides[5] allowing 1-bromo-6-chlorohexane to be converted into 7-chloroheptanoic acid (84%, Table I). Ester and ketone groups are not affected under the reaction conditions.[11] Hence ethyl 5-bromovalerate gave ethyl methyl adipate (95% by gc, Table II) and the steroidal bromo keto ester **4** gave the corresponding methyl ester **5** (71% isolated, eq 6).

While we have not yet explored the stereochemistry of these reactions, the common intermediates involved make it likely that the stereospecificity observed in one of our earlier ketone syntheses[2] will also be found here.



4

5, 71%

(6)

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(10) The alkyl intermediates **3** are unstable in THF (with no HMPA or MP present) at 25° in the concentrations normally used (about 0.25 *M*). Although decomposition is slower at lower temperatures and concentrations, formation of the alkyl intermediates is also slower. Thus the acyl intermediate can normally be prepared from a given halide in higher yield than can the corresponding alkyl intermediate *in THF* (no HMPA or MP added).

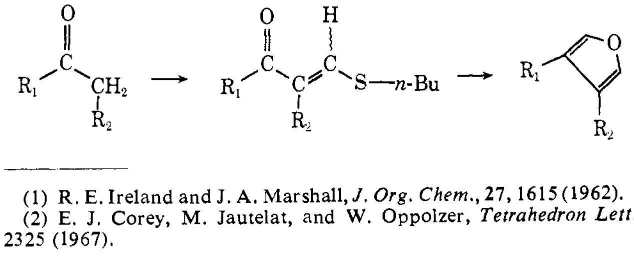
(11) With 5-chloro-2-pentanone neither the acyl or alkyl complex could be formed, apparently due to enolate formation followed by cyclization to methyl cyclopropyl ketone.

A General Method for the Synthesis of 3- and 3,4-Substituted Furans. Simple Syntheses of Perillene and Dendrolasin

Sir:

The reaction of *n*-butylthiomethylene derivatives[1] of ketones with dimethylsulfonium methylide[2] affords good yields of 3- or 3,4-substituted furans. The sequence shown in Scheme I which incorporates this reaction constitutes a widely applicable method for the

Scheme I



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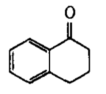
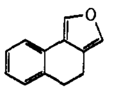
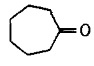
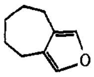
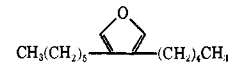
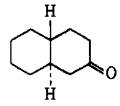
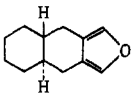
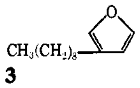
(1) R. E. Ireland and J. A. Marshall, *J. Org. Chem.*, 27, 1615 (1962).

(2) E. J. Corey, M. Jautelat, and W. Oppolzer, *Tetrahedron Lett.*, 2325 (1967).

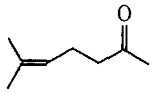
Table I. Synthesis of 3- and 3,4-Substituted Furans

Example	Starting ketone	% yield of *n*-butylthiomethylene derivative[a]	Product[b]	% yield[c]
I		72		65
II		53		62
III	$(CH_3(CH_2)_5)_2C{=}O$	63	 **6**	78
IV		85		58
V	$CH_3(CH_2)_8C({=}O)CH_3$	37[d]		50[d]
VI	**1**	53	**3**	55[e]
VII	**2**	38	**4**	54

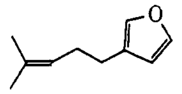
[a] Material suitable for conversion to furan; no attempts were made to optimize these yields. [b] All products had ir and nmr spectra consistent with the assigned structures. In examples I and IV, the products were characterized as solid maleic anhydride adducts which had correct elemental analyses; in examples II, III, and V, structure assignments were confirmed by mass spectra; in examples VI and VII, comparison with data on authentic **3** and **4** confirmed the assignments. [c] Isolated material, homogeneous by tlc, except as noted. [d] Mixed with ~4% of the isomeric product. [e] Yield determined by vpc using an internal standard.

synthesis of these types of compounds from nonfuranoid precursors.[3]

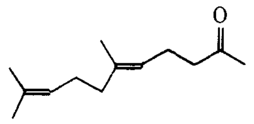
In examples I–III in Table I the structure of the product furan is unequivocally dictated by the structure of the starting ketone; in example IV the well-known tendency for reactions of *trans*-2-decalones to occur at the 3 position prevails. In examples V–VII, the condensation leading to the *n*-butylthiomethylene precursor occurs preferentially at the methyl group,[4] thus providing a selective synthesis of 3-monosubstituted furans.[5] This method accordingly permitted the facile syntheses recorded in Table I of the natural products perillene (**3**)[6] and dendrolasin **4**[7] from the commercially available ketones **1**[8] and **2**,[9] respectively



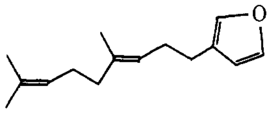
1



3



2



4

Perillene[10] and dendrolasin[10,11] have been synthesized previously by considerably more complicated pathways starting from preformed furans.

A typical procedure for a furan synthesis follows. The α-formyl derivative of 7-tridecanone was prepared by the method of Ainsworth[12] and was converted by the method of Ireland and Marshall[1] to the *n*-butylthiomethylene derivative **5** [ir (film) 6.05 and 6.4 μ; uv max 295 nm (ε 15,000); nmr (CCl_4) δ 0.8–2.0 (m, 27), 2.0–3.0 (m, 6), 7.25 (s, 1)] in 63% overall yield after purification by chromatography on Florisil. To a stirred solution of 4.10 g (2.5×10^{-2} mol) of trimethylsulfonium fluoroborate[13] in 100 ml of anhydrous dimethoxyethane (DME)[14] under nitrogen at −25° was added 10.5 ml of a 2.3 *M* solution of *n*-

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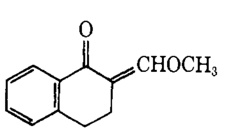
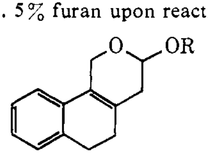
[3] T. M. Harris, C. M. Harris, and J. C. Cleary (*ibid.*, 1427 (1968)) have reported the synthesis of three phenyl-substituted furans by the analogous reaction of methyl enol ethers of 1,3-dicarbonyl compounds with $CH_2S(CH_3)_2$. This is a less satisfactory method because: (1) the enol ether derivatives are much more difficult to purify and handle, and (2) the furan-forming reaction proceeds in lower yield in all cases. For example, i gives 70–80% ii, and *ca.* 5% furan upon reaction with



i



ii, R = H or CH_3

$CH_2S(CH_3)_2$ (*cf.* J. C. Cleary, Ph.D. Thesis, Vanderbilt University 1972, and J. A. Donnelly, P. Bennett, S. O'Brien, and J. O'Grady, *Chem. Ind.* (*London*), 500 (1972), for analogous products incorporating two ylide methylene units.) Products like ii have not been encountered with the *n*-butylthiomethylene derivatives.

[4] See H. O. House, "Modern Synthetic Reactions," 2nd ed, W. A. Benjamin, Menlo Park, Calif., 1972, pp 748–750, for examples. The preference for formylation at the methyl group in examples V–VII in Table I was 8–10 : 1.

[5] Other recent reports of syntheses of 3-alkylfurans include: C. Botteghi and L. Lardicci, *Chim. Ind.* (*Milan*), **52**, 265 (1970); D. Miller, *J. Chem. Soc. C*, 12 (1969); and M. A. Gianturco and P. Friedel, *Can. J. Chem.*, **44**, 1083 (1966).

[6] See, *e.g.*, A. Baggini and M. Pavan, *Tetrahedron Lett.*, 3893 (1967).

[7] See, *e.g.*, M. Pavan, *Ric. Sci.*, **26**, 144 (1956).

[8] K & K Laboratories, Inc., Plainview, N. Y. 11803.

[9] Pfaltz & Bauer, Inc., Flushing, N. Y. 11368.

[10] A. F. Thomas, *Chem. Commun.*, 1657 (1968); *J. Chem. Soc. C*, 220 (1970).

[11] K. A. Parker and W. S. Johnson, *Tetrahedron Lett.*, 1329 (1969).

[12] C. Ainsworth, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 536.

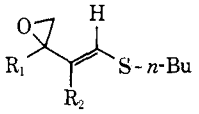
[13] H. Teichmann and G. Hilgetag, *Chem. Ber.*, **96**, 1454 (1963); T. Hashimoto, *et al.*, *Nippon Kagaku Zasshi*, **89**, 810 (1968); *Chem. Abstr.*, **70**, 28546b (1969). Trimethylsulfonium iodide is unsuitable.

[14] Distilled from lithium aluminum hydride directly into oven-dried glassware used for the reaction.

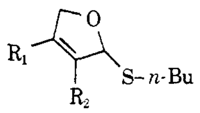
butyllithium in hexane. After standing 15 min at −20° this pale yellow mixture was cooled to −70° and was treated with a solution of 1.49 g (5×10^{-3} mol) of **5** in 15 ml of anhydrous DME. After 1 hr at −70° the yellow mixture was treated with 200 ml of water and extracted with four portions of ether. The ethereal extracts were dried over sodium sulfate, filtered, and evaporated, and the residue was then allowed to stand at room temperature for 24 hr. After this time the product was dissolved in 20 ml of ether and stirred vigorously with 1.30 g of mercuric sulfate for 30 min. This mixture was dried, filtered, and evaporated to afford a black residue which was dissolved in 5 ml of pentane and filtered through 40 g of Florisil. The Florisil was eluted with an additional 300 ml of pentane. Evaporation of the pentane eluents afforded 0.860 g (78%) of 3-*n*-hexyl-4-*n*-pentylfuran (**6**) as a clear oil [ir (film) 8.7, 9.5, and 11.4 μ; uv max 216 nm (ϵ 3300); nmr (CCl$_4$) 0.8–1.8 (m, 20), 2.2–2.5 (t, 4), 7.0 (s, 2)]. Further elution with 50 ml of ether afforded <1% of starting material **5** and ~12% of unidentified, dark, oily material.

In most instances the product furan is accompanied by considerably more (~20–30%) unreacted *n*-butylthiomethylene derivative as the principal and only recognizable contaminant. Despite extensive efforts we have as yet been unable to find a method to ensure complete reaction. Aside from this unresolved difficulty the furan synthesis is quite clean.

The reaction of *n*-butylthiomethylene ketones with CH$_2$S(CH$_3$)$_2$ very probably proceeds by way of intermediates **7** and **8**, analogous to those proposed by Harris[3] in the case of enol ethers of 1,3-dicarbonyl compounds. The product initially formed, before standing for 24 hr, has been found in case V to exhibit nmr spectral properties [nmr (CCl$_4$) 5.4 (d, J = 15 Hz) and 6.2 ppm (d, J = 15 Hz)] consistent with an intermediate epoxide **7** (R$_1$ = CH$_3$(CH$_2$)$_8$; R$_2$ = H). If the final treatment with mercuric sulfate is omitted, dihydrofuran derivatives **8** have been detected spectrally, and **9** has been isolated as a pure oil by preparative tlc (ir (film) 5.80 (w), 5.95 (w), and 9.9 μ (s); nmr (CCl$_4$) 0.7–2.3 (m, 21), 2.47 (t, 2), 4.38 (br s, 2), and 5.65 ppm (br s, 1); M$^+$ (*m/e*) 266.1706 (calcd 266.1704)].



7



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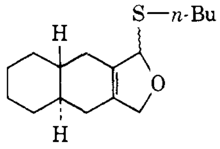

9

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Intramolecular Hydride Shifts in Carbonium Ions

Sir:

Rapid 1,2-hydride shifts are commonly accepted in explanation of a number of rearrangement reactions and in accounting for nmr spectra of several stable carbonium ions. Besides these steps 1,3, 1,4, and 1,5 hydride shifts have also been invoked in a variety of reactions.[1] We wish to report the observation of the nmr spectra of the 2,4-dimethyl-2-pentyl (I), the 2,5-dimethyl-2-hexyl (II), and the 2,6-dimethyl-2-heptyl (III) cations which provide the first *direct* and *quantitative* data on the occurrence of these shifts in the ions themselves.

The ions were each prepared *in vacuo* by forming molecular beams of the corresponding alkyl chloride and antimony pentafluoride and impinging them on a surface cooled to liquid nitrogen temperature.[2] The resulting mixture was dissolved in SO$_2$ClF at −115° and was transferred to nmr tubes which were then sealed.

The nmr spectrum at −114° for ion I is shown in Figure 1A and is similar to that described by Brouwer.[3] The methylene protons appear as a broad peak at τ 5.94, and the α- and γ-methyl protons give rise to a broadened singlet and doublet at τ 6.13 and 8.68, respectively. Spin decoupling showed the unresolved multiplet at τ 6.92 to be due (at least in part) to the methine proton. In addition, traces of *tert*-butyl (sharp singlet at τ 6.08) and 2,3-dimethylpentyl cation (peaks at τ 7.20, 7.35, and 8.45) were also present.

Upon warming, the methyl peaks of ion I broaden and at approximately −90° coalesce to give a single peak centered near τ 7.4. In this temperature range, the methylene protons undergo no noticeable change. The reaction therefore cannot proceed *via* successive 1,2-hydride shifts. A complete line-shape analysis, assuming the 1,3-hydride shift, yields an activation energy of 8.5 ± 0.1 kcal/mol with a log A of 12.6 ± 0.1.

The spectrum of carbonium ion II (Figure 1B) at −95° consists of peaks at τ 5.88 and 8.13 for the α- and β-methylene protons and τ 6.18 and 8.80 for the α- and δ-methyl protons. As reported by Brouwer,[3] line broadening due to hydride shifts was absent up to −55°. (Above this temperature, the spectrum becomes more complicated due to rearrangement to the isomeric tertiary cations.) However, by using the magnetization transfer technique,[4] it was shown that a 1,4-hydride shift does occur in the ion, and that the energy required for the transfer is in the vicinity of 12–13 kcal/mol. This

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(1) J. L. Fry and G. J. Karabatsos in "Carbonium Ions," Vol. 2, G. Olah and P. Schleyer, Ed., Wiley-Interscience, New York, N. Y., 1970, p 521.

(2) M. Saunders and D. Cox, "A Molecular Beam Technique for Preparing Carbonium Ions," submitted for publication, *J. Amer. Chem. Soc.*

(3) D. M. Brouwer and J. A. van Doorn, *Recl. Trav. Chim. Pays-Bas*, **88**, 573 (1969).

(4) R. A. Hoffmann and S. Forsen, *Progr. Nucl. Magn. Resonance Spectrosc.*, **1**, 15 (1966).